PI(s) of MSM U01: Muhammad H. Zaman and Roger D. Kamm
Institution(s): Boston University and Massachusetts Institute of Technology
MSM U01 Grant Number: U01 CA177799
Title of Grant: Modeling Bi-Directional Signaling And Cytoskeletal Dynamics In 3D Cell Migrations

Abstract Authors

R.J. Seager, Fabian Spill, Ran Li, Roger D. Kamm, Muhammad H. Zaman

Abstract Text

Title: Synergistic interactions between TGF-β1- and TNFα-induced signaling in cancer cells are the result of TAK1- and Smad7-mediated crosstalk

A tumor is not a homogenous mass of cancer cells, but is in fact a diverse microecosystem populated by many physical, chemical, and biological actors, all of which interact with each other and, together, drive gross tumor behavior. When small signaling molecules known as cytokines are expressed and secreted from a cell into the extracellular space, they can bind to corresponding receptors on the same cell or other cells, initiating intracellular signaling pathways capable of affecting many cell processes and behaviors. Two cytokines expressed and secreted by tumor-associated macrophages (TAMs), transforming growth factor-β1 (TGF-β1) and tumor necrosis factor-α (TNFα), have been shown to modulate the speed and directedness of cancer cell migration, as mediated by changes in the extracellular matrix (ECM)-degrading enzymes membrane-type-1 matrix metalloproteinase (MT1-MMP) and matrix metalloproteinase-1 (MMP1), respectively. These expression changes—and thus the migration effects—are driven by a nonlinear signaling network characterized by extensive crosstalk between the downstream intracellular signaling pathways activated by these cytokines, where migration directedness is controlled by a synergistic integration of TGF-β1 and TNFα activity and migration speed is more directly regulated by TGF-β1 activity alone. In order to elucidate the intracellular signaling mechanisms and species responsible for these behaviors, we have constructed an ordinary differential equation signaling model describing the TGF-β and TNFα signaling pathways in cancer and how they interact, and used this model to reproduce and explore the mechanisms underlying the observed synergistic interaction between the two pathways. From this computational analysis of these pathways, we determined the connection points between the TGF-β and TNFα signaling pathways that facilitate this behavior, demonstrated the ability of our model to reproduce experimental observations, explored the mechanisms underlying this ability, and showed that in the absence of these mechanisms the observed signaling behavior cannot be recaptured. In particular, we showed how TGF-β-activated kinase 1 (TAK1), an intermediate signaling protein indirectly activated by both TGF-β1 and TNFα, serves as an integrator of TGF-β and TNFα signaling, and Smad7, a transcriptionally-regulated signaling protein, serves as a mutually regulated inhibitor of both pathways, facilitating the observed signaling. Finally, we conducted sensitivity analyses to explore other signaling species exerting significant control over cytokine-regulated MMP expression. By analyzing this system through mathematical modeling methods, we hope to gain a broader understanding of how TAM-induced cytokine signaling affects cancer cell behavior and demonstrate the utility of these methods in cancer biology.